

Serial No.: 08/469,492
Examiner: P. Duffy

REMARKS

Reconsideration of this application is respectfully requested.

Following entry of this Amendment, claims 37-39, 42-49, 52-57 and 59-65 will be pending. Claims 48-49 and 52-56 have been amended.

Claims 37-39, 42-49, 52-57 and 59-65 stand rejected under 35 U.S.C. § 112, first ¶, for lack of enablement, and claims 48-49, 52-55 and 56, 62, 63 and 64 stand rejected as anticipated by the Merck Manual under 35 U.S.C. § 102(b).

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 37-39, 42-49, 52-57 and 59-65 stand rejected under 35 U.S.C. §112, first ¶, as lacking enablement. The Examiner states that: (i) the prior art teaching of the rat and mouse GAD cDNA and methods for GAD protein purification (in combination with the teachings of the present specification) is not sufficient to enable a person of skill in the art to make and use this antigen in a method of treatment of the present invention; (ii) the results in the specification based on animal models are not predictive of the success of the present treatment in humans, and (iii) Tian *et al.* reference (which shows successful nasal administration of GAD to induce Th2 response and prevent Type I diabetes) fails to support enablement of claims directed to administration of GAD *after* the onset of the autoimmune disease. This rejection is respectfully traversed.

Serial No.: 08/469,492
Examiner: P. Duffy

Applicants respectfully submit that the Examiner has failed to give proper weight to the evidence submitted with the Amendment mailed March 31, 1997 with respect to whether a person of skill in the art would have been able to make and use the invention in view of the guidance in the specification and general knowledge in the art with respect to GAD.

The Examiner states that a person of skill in this art would not administer a protein from another species (*i.e.*, rat or mouse) to a human due to possible immunological problems that may arise as a result of such administration. This rejection is essentially based on safety concerns that may arise when a non-human compound is administered to humans. It is well established, however, that safety concerns are not properly within the scope of patent examination:

[I]t is improper for Office personnel to request evidence of safety in the treatment of humans. ... Congress has created a special agency to determine both the safety and effectiveness of new drugs. That agency is Food and Drug Administration (FDA).

See Legal Analysis Supporting Utility Examination Guidelines, PAT., TRADEMARK AND COPYRIGHT J. (BNA), 50: 295, at 308, 1st full ¶ and footnote 67 (1985). It is therefore submitted to be irrelevant, for purposes of the present examination, whether rat or mouse GAD administered to a human would cause immunologic problems. In fact, it is well known that even FDA approved drugs often entail certain risks or have undesirable side effects. The enablement rejection is thus not properly based on this ground.

Serial No.: 08/469,492
Examiner: P. Duffy

The Examiner also states that there is "no evidence that administration of any specific bystander antigen when administered as instantly claimed is therapeutically effective in humans" (Official Action, page 4). Specifically, the Examiner doubts that the results in the specification based on animal mouse models (*e.g.* EAE and NOD) are predictive of treatment in humans relying on the results of Phase III Myloral trials (reported in *BioWorld Today*, 8(77):1,3). The Examiner states that human results were negative although animal results indicated that myelin would be effective at treating MS in humans and concludes that results from animal models in general "do not *a priori* predictably and reproducibly correlate with human response" (Official Action, page 4). Applicants respectfully disagree for the reasons outlined below.

It is submitted that the results of the Myloral Phase III trials do not show that myelin administration is ineffective, as discussed in detail in the enclosed declaration of Dr. Malcolm Fletcher ["Fletcher Declaration"] (Tab 1). On the contrary, it is submitted that the results from this and prior trials are encouraging and clinically meaningful and that further trials should be performed (Fletcher Declaration, ¶¶ 9, 11). For example, Exhibit I (attached to the Fletcher Declaration; an additional more legible copy of Exhibit I is also enclosed) shows the annual attack rate before and after treatment in the U.S. Phase III clinical trials of four multiple sclerosis drugs. Three of these drugs (Betaseron, Avonex, and Copaxone) have already been approved for commercial sale in the U.S. for treating multiple sclerosis. The results depicted in the graph establish that the annual attack rate for multiple

Serial No.: 08/469,492
Examiner: P. Duffy

sclerosis patients who received Myloral in the AutoImmune Phase III clinical trial decreased substantially in comparison to the control (Fletcher Declaration, ¶ 6). Furthermore, use of the Myloral composition resulted in approximately the *same* reduction in attack rate as for each of the three approved drugs. However, this beneficial effect of Myloral was masked by a strong placebo effect which is believed to be a result of the fact that Myloral has no side effects and therefore the patients could not determine if they were receiving a placebo or an active agent (Fletcher Declaration, ¶ 7). Beneficial effects of Myloral are also seen when myelin is administered in combination with beta-interferon (Fletcher Declaration, ¶ 8 and Exhibit II). Additional encouraging magnetic resonance imaging results measuring lesion load were obtained with respect to a particular genetic subgroup of patients treated with Myloral (Fletcher Declaration, ¶ 10). Based on this, Dr. Fletcher concludes that the Phase III Myloral results do not indicate lack of efficacy, but are encouraging data (Fletcher Declaration, ¶ 12). This supports the conclusion that there is a reasonable correlation between the data obtained using the EAE model and the human results.

Also, since the Examiner asserts that the specification fails to provide sufficient evidence that the invention is effective in humans, the rejection (although brought under Section 112, first ¶) appears to be a rejection based on lack of utility. In effect, the Examiner is asserting that the method described in the specification is not useful for treating humans. However, Applicants submit that the Examiner has failed, as required, to establish a *prima facie* showing that the invention has no utility.

Serial No.: 08/469,492
Examiner: P. Duffy

To establish a *prima facie* showing that the invention as claimed does not work as taught in the specification, the Examiner:

must articulate sound reasons why a person of ordinary skill in the art would conclude that it is *more likely than not* that the asserted utility [here, administering bystander antigens by inhalation to treat an autoimmune disease in humans] is not credible.

See Utility Examination Guidelines, PAT., TRADEMARK AND COPYRIGHT J. (BNA), 50: 295, at 305, 1st ¶ (1985). Furthermore, the Examiner should provide evidence (preferably documentary evidence) in support of the *prima facie* showing. Here, the Examiner has not provided any basis to doubt that therapeutic treatment described in the present specification is effective. As discussed above, the Phase III Myloral results are not properly interpreted to mean that the EAE model is not predictive of utility in humans.

It is respectfully submitted that the statement that "mouse models do not *a priori* predictably and reproducibly correlate with an appropriate human response" does not meet the above criteria of a *prima facie* showing. The standard is whether a person of skill in the art would have considered the results obtained in animal models *reasonably predictive* of the success in humans. A person of ordinary skill in the art would have concluded that it is more likely than not that the method described in the specification can be used to treat autoimmune diseases because EAE and NOD mouse systems are standard experimental models recognized in the art as useful for testing immunosuppressants.

Serial No.: 08/469,492
Examiner: P. Duffy

[I]nherent in the concept of the 'standard experimental animal' is the ability of one skilled in the art to make the appropriate correlation between the results actually observed and the probable results in human therapy.

See Legal Analysis Supporting Utility Examination Guidelines, PAT., TRADEMARK AND COPYRIGHT J. (BNA), 50: 295, at 307, footnote 63 (1985). The fact that results in clinical trials (once available) may not correlate with animal data is not dispositive.

As discussed above, the Phase III Myloral results tended to *confirm* that the EAE model results are reasonably predictive of treatment effectiveness in humans. In addition, applicants submit herewith a copy of a declaration by Dr. George Eisenbarth ["Eisenbarth Declaration"] establishing why the NOD mouse model is also a recognized animal model frequently used to study autoimmune diabetes (Tab 2). Eisenbarth Declaration was submitted in U.S. Application Ser. No. 07/595,468 to establish that NOD mouse system is a recognized model for testing immunosuppressive drugs and to overcome a rejection similar to that in the present application. Dr. Eisenbarth states that the NOD mouse model is "the best model of Type 1 diabetes available" (Eisenbarth Declaration, ¶ 10). The model has been used to test effectiveness of many drugs including cyclosporin A, now a recognized nonspecific immunosuppressant (Eisenbarth Declaration, ¶ 10). Based on the Eisenbarth Declaration and evidence submitted therewith, the Patent and Trademark Office withdraw the rejection in the '468 application on the same basis. For the same reasons, the present rejection should also be withdrawn.

Serial No.: 08/469,492

Examiner: P. Duffy

By dismissing animal mouse models as *a priori* unpredictable, the Examiner has left Applicants with a single option for overcoming the rejection: submission of human clinical data. Such an implicit request for clinical data is strongly advised against by the Utility Guidelines. The enablement rejection should be therefore withdrawn.

However, to further demonstrate that bystander suppression is, in fact, an effective mechanism for suppressing autoimmune response, Applicants submit herewith a publication by Von Herrath *et al.* (*J. Clin. Invest.* 96(6):1324-1331; 1996) (Tab 3). Von Herrath *et al.* confirm the effectiveness of bystander suppression in another model of Type I diabetes, *i.e.*, virally induced diabetes in transgenic mice.

The Examiner also states that the Tian *et al.* reference (*J. Exp. Med.*, 183:1561-1567; 1996) fails to support enablement of the present claim 47, directed to a method of treating Type I diabetes by administering GAD by inhalation, because Tian *et al.* teach nasal administration of GAD before the onset of autoimmunity. The Examiner states that "[o]nly when the peptides are administered before the onset of autoimmunity is any affect observed" (Official Action, page 4).

While the Tian reference describes experiments which establish that nasal administration of GAD can prevent Type I diabetes, Applicants submit that there is nothing in the reference to suggest that nasal administration of GAD is *only* effective when administered prior to the onset of the disease. There are no experimental data in the Tian reference to support the Examiner's conclusion that nasal administration of GAD would not

Serial No.: 08/469,492
Examiner: P. Duffy

be effective after the onset of the disease. Furthermore, Tian *et al.* teach that "nasal administration of GAD65 peptides interferes with the development of the diabetogenic process through induction of a Th2 response (active tolerance)" (page 1565, col. 2, 3rd ¶). Applicants submit that the art teaches no reason to expect that Th2 responses would not have a beneficial suppressive effect on the Th1 (disease-associated) response *after* the onset of the disease. Tian nowhere suggests that Th2 responses could no longer be induced after the autoimmune stage of Type I diabetes has commenced.

In view of the above remarks, applicants respectfully request that the Examiner withdraw the rejection of claims 37-39, 42-49, 52-57 and 59-65 under 35 U.S.C. §112, first paragraph for lack of enablement.

REJECTION UNDER 35 U.S.C. §102

Claims 48-49, 52-55 and 56, 62, 63 and 64 stand rejected under 35 U.S.C. §102(b) as anticipated by pages 1087-1088 of the Merck Manual. The Examiner states that the Merck Manual discloses a composition of glucagon in a pharmaceutically acceptable diluent, which (although intended for parenteral administration) can be used for topical, nasal or oral administration. Applicants respectfully traverse this rejection.

The Examiner essentially asserts that the parenteral solution containing glucagon inherently is a dosage form of the present invention.

Serial No.: 08/469,492
Examiner: P. Duffy

Claims 48-49, 52-55 and 56, 62, 63 and 64, as amended, do not merely call for a solution containing glucagon but are directed to dosage forms "adapted for nasal or mouth administration." The parenteral solution cited is submitted to be clearly distinguished by this language.

The Merck Manual discloses a vial containing glucagon in powdered form and a solution suitable for parenteral administration, but does not disclose any dosage forms for nasal or mouth administration, *e.g.* one in an aerosol form. For this reason, claim 52 is separately patentable over the Merck Manual.

Withdrawal of the rejection of claims 48-49, 52-55 and 56, 62, 63 and 64 under 35 U.S.C. §102(b) as anticipated by the Merck Manual is respectfully requested in view of the above remarks.

CLAIM OBJECTIONS

The Examiner has objected to claims 37, 39 and 65, on the grounds that claims 37 and 39 are identical and that claim 65 does not differ in scope. Applicants respectfully traverse this objection.

Claim 37 calls for administering a bystander antigen which is not an autoantigen in the particular human being treated (but may be an autoantigen in another human). Claim 39 is of different scope and calls for administering a bystander antigen which is not an autoantigen in any human. A good illustration of this distinction is provided in

Serial No.: 08/469,492
Examiner: P. Duffy

Example 6 of the specification, which discloses a method of treating PLP-induced EAE by administering MBP. Although MBP is an autoantigen in MBP-induced EAE, it is not an autoantigen in a PLP-induced EAE.

Applicants submit with respect to claim 65, that they are entitled to claim the same invention in more than one way.

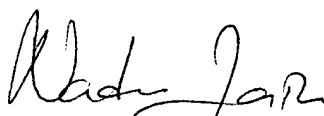
Withdrawal of the objection is respectfully requested.

CONCLUSION

It is submitted that the pending claims are now in condition for allowance.

Issuance of a Notice to that effect is earnestly solicited.

Respectfully submitted,

 Reg. No 41,431

Seth H. Jacobs
Registration No. 32,140
Attorney for Applicants

DARBY & DARBY P.C.
805 Third Avenue
New York, New York 10022
(212) 527-7700